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Phosphoranyl Radical Fragmentation Reactions Driven by Photoredox Catalysis

James A. Rossi-Ashton,* Aimee K. Clarke, William P. Unsworth, and Richard J. K. Taylor



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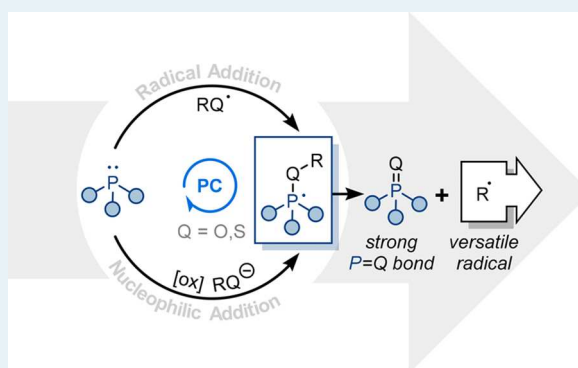
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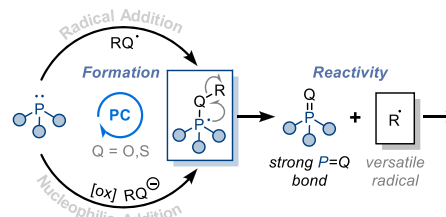
ABSTRACT: Photocatalytic generation of phosphoranyl radicals is fast emerging as an essential method for the generation of diverse and valuable radicals, typically via deoxygenation or desulfurization processes. This Perspective is a comprehensive evaluation of all studies using phosphoranyl radicals as tunable mediators in photoredox catalysis, highlighting how two distinct methods for phosphoranyl radical formation (radical addition and nucleophilic addition) can be used to generate versatile radical intermediates with diverse reactivity profiles.

KEYWORDS: phosphoranyl, radical, photoredox, visible light, phosphine



Phosphines and their derivatives are among the most important class of reagents in synthetic chemistry. Most established synthetic methods that utilize phosphines operate via ionic, two-electron processes.¹ Contrastingly, the chemistry of phosphine-derived radicals has been less well explored.² The analogous radical chemistry of amines and their derivatives (whose valency is equivalent to that of phosphines) has been investigated much more widely, not least in photoredox catalysis, and this topic has been extensively reviewed.³ However, radical phosphine chemistry is undoubtedly an increasingly active area of research,² and notably the chemistry of phosphoranyl radicals has received much recent attention. This can be accredited to the application of phosphoranyl radicals as an important, tunable strategy to access diverse radical species, typically via deoxygenation or desulfurization processes, with the resurgence of this area clearly linked to the rapid development of photoredox catalysis in the past decade.⁴ Considering the diverse array of useful synthetic transformations, phosphoranyl radical-mediated chemistry has been shown to enable, a critical summary and outlook of this quickly advancing area will be helpful for its continued development. Therefore, this Perspective is a comprehensive evaluation of all studies that use phosphoranyl radicals as tunable mediators in photoredox catalysis, highlighting how two distinct methods for phosphoranyl radical formation (radical addition and nucleophilic addition) can be used to generate versatile radical intermediates with remarkably diverse reactivity profiles (Scheme 1).

Scheme 1. Phosphoranyl Radical-Mediated Generation of Versatile Radical Intermediates



EARLY DETECTION AND REACTIVITY STUDIES

Before addressing phosphoranyl radicals in photoredox catalysis, it is instructive to consider earlier studies based on more classical radical chemistry, which also includes various photochemical processes. Phosphoranyl radicals were first proposed as intermediates in the late 1950s,⁵ subsequently detected for the first time by ESR spectroscopy in the 1960s,⁶ and finally isolated and characterized by single-crystal X-ray diffraction in 2013.⁷ They are formally tetravalent phosphine-

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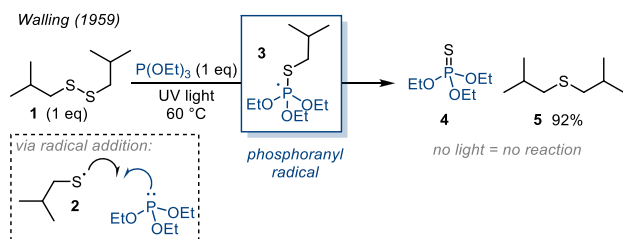
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centered radicals, although the exact nature of the radical is unclear.⁸

Hoffmann and then Walling first explored the reactivity of phosphoranyl radicals in 1956^{5a} and 1957,^{5b} respectively. Both groups disclosed desulfurization reactions using either light⁹ or heat in the presence of $P(OEt)_3$ as routes to prepare sulfide and thiophosphate products via a phosphoranyl radical intermediate. For example, in Walling's work (Scheme 2),^{5b,c}

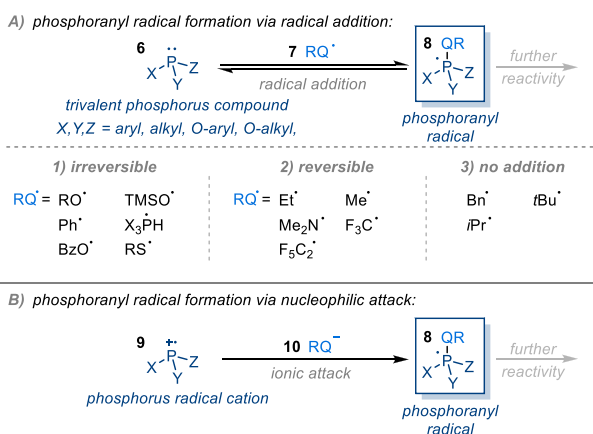
Scheme 2. Early Phosphoranyl Radical Reactivity^{5c}



thiyl radicals **2**, generated in situ from the homolysis of disulfides **1** under UV light irradiation, were found to couple with $P(OEt)_3$, affording phosphoranyl radicals (e.g., **3**). These phosphoranyl radicals then underwent either radical fragmentation (via β -scission, see later) or single-electron oxidation by another thiyl radical, with both pathways leading to the formation of the same thiophosphate **4** and sulfide **5** products.

Since these early studies, several other methods for the formation of phosphoranyl radicals have been documented. The most common method for their formation is radical addition into a trivalent phosphorus species, typically a phosphine, or phosphite (Scheme 3A).¹⁰ Alternatively, the equivalent phosphoranyl radical can also be generated via ionic attack of a trivalent phosphorus radical cation with a suitable nucleophile (Scheme 3B).¹¹

Scheme 3. Phosphoranyl Radical-Formation Pathways

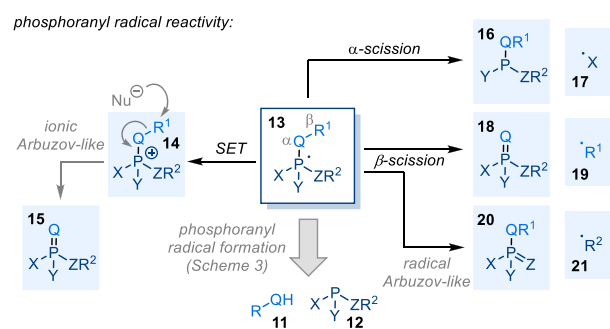


Bentrude and co-workers extensively investigated the formation of phosphoranyl radicals via radical addition (Scheme 3A) during the 1970s¹² and classified these additions into three distinct pathways: (1) radicals **7** that react with trivalent phosphorus species **6** irreversibly and exothermically with a near diffusion-controlled rate; (2) radicals that react reversibly with trivalent phosphorus species, but require rapid α - or β -scission fragmentation to drive the reaction to any product; (3) radicals that form very weak bonds to phosphorus and so do not react, even reversibly. Which of these three

possible pathways operate is attributed to the relative stabilities and bond strengths of the intermediates formed; for example, the alkoxide radicals (RO^\bullet , $TMSO^\bullet$, BzO^\bullet) populate classification **1**, largely due to the strong P–O bond that is formed upon addition (P–O bond 340 kJ mol^{-1} vs P–C bond 305 kJ mol^{-1}),¹³ which acts as a strong thermodynamic driving force. For more detail regarding radical addition into phosphorus, see references **12a** and **14**.

Phosphoranyl radical-forming reactions that proceed via ionic attack from a suitable nucleophile (Scheme 3B) typically operate under stoichiometric conditions, and therefore, the intermediate phosphoranyl radical **8** is usually quickly oxidized (cf. **13** \rightarrow **14** Scheme 4) before other, often more desirable,

Scheme 4. Phosphoranyl Radical Reactivity Pathways

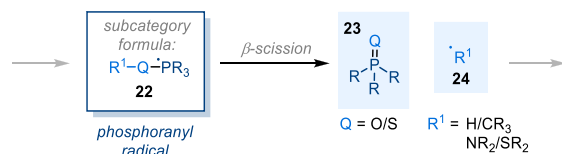


phosphoranyl radical reactivity can occur.¹¹ However, by controlling the concentration of oxidizing species throughout the reaction by way of photoredox catalysis, these other reactivity pathways can be accessed and used to drive productive chemistry; this is arguably one of the key advantages of photoredox catalysis in this field and is important in enabling much of the innovative chemistry described in this Perspective.

The reactivity of phosphoranyl radicals has been comprehensively studied spectroscopically, and they have been shown to react via various pathways, including direct oxidations and radical reactions; however, the most important processes proceed via α - or β -fragmentation (Scheme 4).^{12,14} Direct oxidation proceeds via single electron transfer (SET) with a suitable oxidant to afford phosphonium ion **14**, which can then react further via ionic, Arbuzov-type reactions, to form a phosphine oxide or phosphate **15**, depending on the substituents. Alternatively, α - or β -scission fragmentation pathways can occur; α -scission leads to the formation of a new trivalent phosphorus species **16** and a radical **17** derived from the initial phosphorus species **12**, resulting in a net substitution reaction on phosphorus. In contrast, β -scission results in the formation of phosphine oxide/phosphate **18** and a new radical **19**, itself derived from the initially attacking radical or nucleophile **11**. In rarer cases, β -scission can also occur from a resident group of the initial phosphorus species **12**, rather than from the incoming radical or nucleophile in a radical Arbuzov-like reaction, forming phosphine oxide/phosphate **20** and a new radical **21**. The competition between α - and β -scission is largely dictated by the relative radical stabilities of the phosphoranyl radical and possible leaving groups, although the relative bond strengths of the products also have a strong influence on the observed product distribution.

Although there have been many studies focused on the identification and characterization of phosphoranyl radical intermediates, they have been used far less frequently in synthetic chemistry until relatively recently, when various synthetic applications of phosphoranyl radical intermediates have been reported, employing a variety of radical initiation processes (including numerous, important, nonphotocatalytic processes such as chemical/thermal,^{10e-m} photochemical,^{10b,c} electrochemical,^{11c-e} etc.). However, this Perspective is focused on photocatalytically initiated transformations that proceed via single-electron transfer processes (i.e., photoredox)¹⁵ as the majority of recent methodologies fall within this category and thus share comparable mechanistic aspects. Selected examples of other photocatalytic processes (e.g., photosensitization) have been included where they were deemed to be especially relevant. These photocatalytic processes are described below and are categorized by (1), whether the reaction is proposed to proceed via a photocatalytically generated radical reacting with a phosphine derivative (cf. Scheme 3A) or (2), whether a nucleophile is reacting with a photocatalytically generated trivalent phosphorus radical cation (cf. Scheme 3B). All phosphoranyl radicals described in this Perspective undergo subsequent β -scission fragmentation pathways, and therefore, the two categories detailed above are further subcategorized by the nature of the bond cleaved in the β -scission fragmentation process and consequently the nature of the radical thus formed (Scheme 5). For example, C–O– \cdot PR₃, represents the cleavage of the C–O bond and the formation of a C-centered radical.

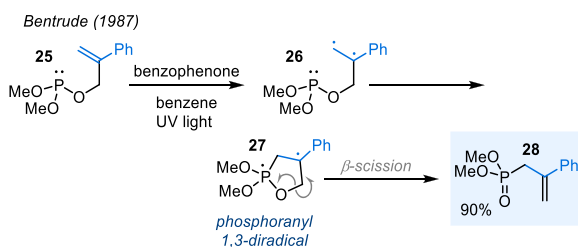
Scheme 5. β -Scission Fragmentation Subcategory Format



RADICAL ADDITION INTO A PHOSPHINE DERIVATIVE

C–O– \cdot PR₃ Fragmentation. Some of the earliest work into the photocatalytic generation of phosphoranyl radical intermediates was conducted by Bentrude and co-workers (Scheme 6).¹⁶ As far back as 1987, these authors used the photosensitization of alkenes **25** tethered to phosphites, to generate carbon-centered radicals **26** that undergo electrocyclic intramolecular rearrangements. A range of photosensitizers were explored, including benzene, *p*-xylene, and benzophenone, all of which increased the yield and conversion of the reaction relative to the analogous reaction without a photo-

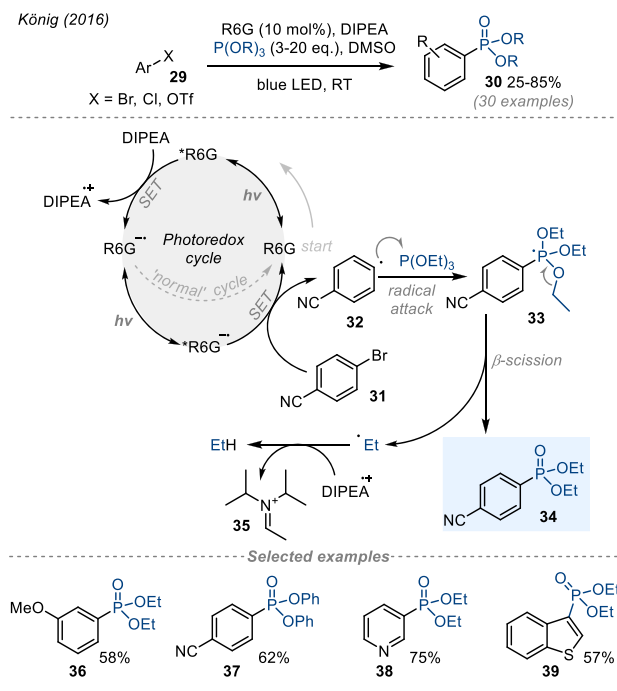
Scheme 6. Photosensitization Rearrangement¹⁶



sensitizer. The group went on to explore other related photoinduced intramolecular rearrangements,^{17,18} including a photoredox variant reported in 1993, which proceeded via a SET-initiation, using 9,10-dicyanoanthracene (DCA) as the SET agent.^{17a}

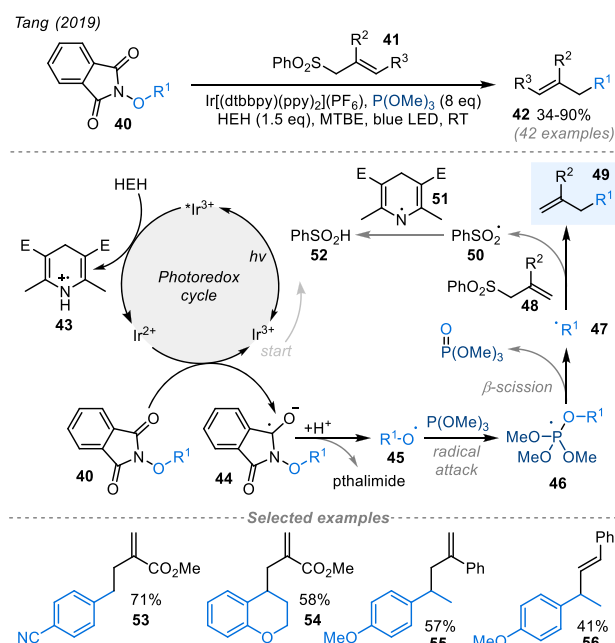
In 2016, following these earlier works, and aided by modern advances in photoredox catalysis, König and co-workers reported the synthesis of aryl phosphonates **30** from aryl halides and pseudo halides **29** and P(OEt)₃ via phosphoranyl radical **33**, under photocatalytic conditions (Scheme 7).¹⁹ The

Scheme 7. Aryl Radical Phosphonation¹⁹



photocatalyst employed, rhodamine 6G (R6G), has the unusual property of undergoing consecutive photoinduced electron transfer;²⁰ excited state photocatalyst [\cdot R6G] undergoes SET with DIPEA to generate the reduced radical anion [$R6G^{\bullet-}$], which in a “normal” photocatalytic cycle would then reduce a suitable substrate, but in this pathway, the radical anion [$R6G^{\bullet-}$], can then absorb an additional photon of light to become an excited state radical anion [\cdot R6G $^{\bullet-}$]. This second excited state has a very high reducing potential ($E^*_{ox} = -2.4$ V vs SCE) relative to the ground state radical anion ($E_{ox} = -1.0$ V vs SCE). König utilizes this highly reducing state to promote SET with an aryl bromide **31**, affording an aryl radical **32** that then reacts with P(OEt)₃ to generate phosphoranyl radical **33**.²¹ Phosphoranyl radical **33** then undergoes β -scission to form product **34** and an ethyl radical, which undergoes hydrogen atom transfer (HAT) to generate ethane (note that this mechanism proceeds via the less common, radical Arbuzov-like β -scission pathway discussed earlier, see Scheme 4). Several other groups have also reported similar processes to König (Scheme 7), whereby photocatalytically generated aryl radicals add into phosphites resulting in the formation of phosphonates.²²

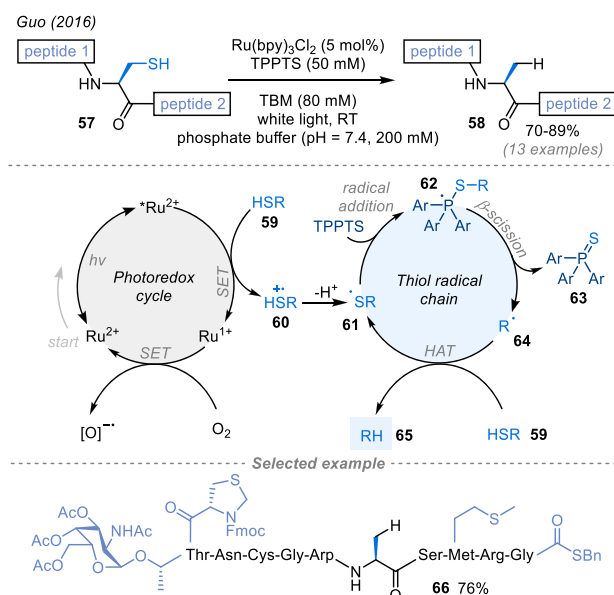
In 2019, Tang and co-workers reported the deoxygenation of *N*-alkoxyphthalimides **40** via phosphoranyl radical **46**, to afford a range of functionalized alkenes **42** using an iridium(III) photocatalyst (Scheme 8).²³ The excited state

Scheme 8. Benzylic Radical Alkylation²³

photocatalyst (Ir^{3+}) is first reduced by Hantzsch ester (HEH) to afford a highly reducing, ground state, Ir^{2+} species. This then undergoes SET with *N*-alkoxyphthalimide **40**, and after protonation by Hantzsch ester radical cation **43**, affords an alkoxyl radical **45** and phthalimide. This alkoxyl radical **45** can easily undergo β -fragmentation or hydrogen abstraction, however, in the presence of $\text{P}(\text{OMe})_3$, addition occurs to form phosphoranyl radical **46**, which then undergoes β -scission to give alkyl radical **47**. The released alkyl radical **47** has then been shown to react with an array of allyl and alkenyl sulfones **48**, furnishing alkene products **49** alongside benzenesulfonyl radical **50** via an addition–elimination sequence. Benzenesulfonyl radical **50** then undergoes HAT process to form sulfinic acid **52**. While the focus of this study was the formation and application of benzylic radicals, several other types of alkyl radical were shown to be tolerated by the reaction, although the corresponding products were formed in diminished yields. Judicious choice of the phosphite and its use in high excess were required to suppress deleterious HAT reactions of alkoxide radical **45** that would lead to the formation of the corresponding alcohol.

It is also worth noting that Schmidt and co-workers have described numerous procedures whereby *N*-hydroxyphthalimides are converted into the corresponding phthalimidyl radicals via a HAT/phosphite-promoted radical deoxygenation process (comparable to Scheme 8). These phthalimidyl radicals, generated in situ, were shown to react with a range of different radical acceptors. However, these important studies are not dealt with in detail within this Perspective, as in each case the group employ a thermal radical generation method.^{10h–m}

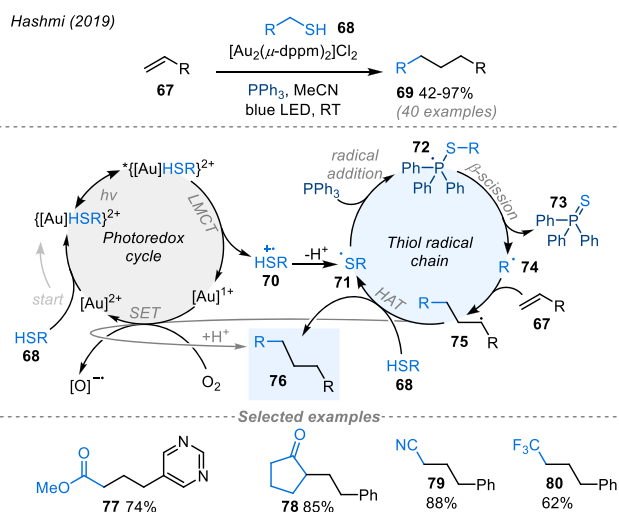
C–S– PR_3 Fragmentation. In 2016, Guo and co-workers reported a visible-light initiated desulfurization method using $\text{Ru}(\text{bpy})_3\text{Cl}_2$ as the photocatalyst (Scheme 9).²⁴ The study focused on the desulfurization of cysteinyl peptides **57** and was compatible with the presence of other amino acid residues and sulfur-containing functional groups. The reaction was performed in either aqueous solution or a binary mixture of

Scheme 9. Peptide Desulfurization²⁴

aqueous/organic solvent and consequently, the phosphine source used was 3,3',3''-phosphinidynetris(benzenesulfonic acid) trisodium salt (TPPTS) because of its solubility in water. *t*Butyl mercaptan (TBM) was also used as a scavenger reagent. Analogous to the works of Hoffmann and Walling (cf. Scheme 2), the authors propose that the reaction proceeds initially via excitation of the photocatalyst into its photoexcited state (Ru^{2+}) which oxidizes thiol **59**, thus forming thiyl radical **61** after deprotonation. Thiyl radical **61** then couples with the phosphine to afford phosphoranyl radical **62** and undergoes β -scission to form alkyl radical **64**, which can then abstract hydrogen from another molecule of thiol present in the reaction.

Danishefsky and co-workers have also reported a related procedure for the desulfurization of peptides, using a similar phosphoranyl radical procedure; however, this work is not described in this Perspective as this process uses thermal initiation.²⁵

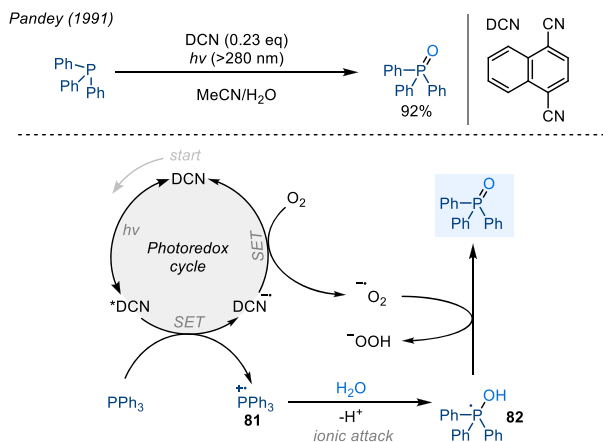
In 2019, Hashmi and co-workers reported a gold photocatalyst-mediated desulfurization/alkylation reaction that has been demonstrated in the synthesis of a range of functionalized alkanes **69**, with the reaction proceeding via phosphoranyl radical **72** (Scheme 10).²⁶ On its own, $[\text{Au}_2(\mu\text{-dppm})_2]\text{Cl}_2$ requires UVA light to undergo photoexcitation, but coordination of thiol **68** generates a complex in situ, that is able to undergo photoexcitation promoted by visible light. Thus, the visible light photoexcited species $[\text{Au}(\mu\text{-dppm})_2\text{HSR}]^{2+}$ then releases oxidized thiol intermediate **70** via a proposed ligand-to-metal charge transfer process. Upon deprotonation, thiyl radical **71** couples with PPh_3 to afford phosphoranyl radical **72**, which then undergoes β -scission to afford alkyl radical **74** and reacts further with a styrene radical acceptor **67** to afford alkyl radical **75**. Radical **75** can undergo one of two pathways; (1) reduction from the reduced ground state photocatalyst $[\text{Au}]^{1+}$, to close the photoredox cycle (the photoredox cycle can alternatively be closed via reduction of O_2), and affording product **76** after protonation or (2) a HAT process with another thiol molecule **68** to afford alkyl product **76** and thiyl radical **71**, thus propagating the thiol radical chain.

Scheme 10. Desulfurization/Alkylation Cascade²⁶

Shortly after this work was published, Jiao and co-workers disclosed a nonphotocatalytic variant of this reaction, using AIBN as the radical chain initiator.^{10j}

■ NUCLEOPHILE ADDITION INTO A PHOSPHORUS RADICAL CATION

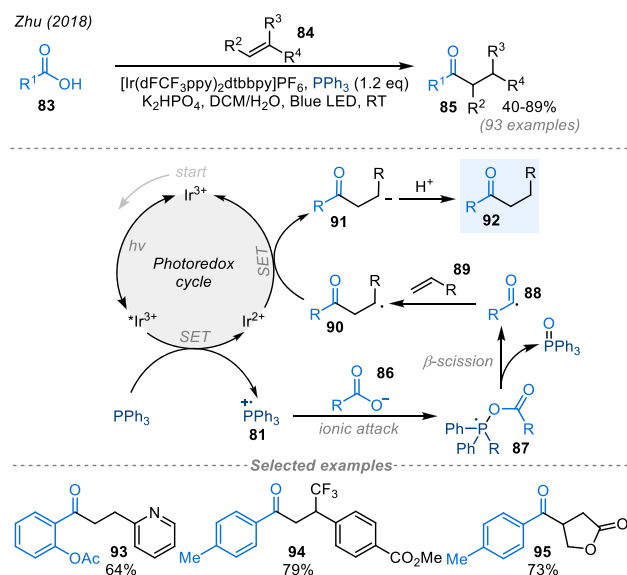
H–O–*PR₃ Fragmentation. Pandey and co-workers first reported a photocatalyzed oxidation of triphenylphosphine to triphenylphosphine oxide in 1991 (Scheme 11).²⁷ Photo-

Scheme 11. Radical Triphenylphosphine Oxide Formation²⁷

excitation of dicyanonaphthalene (DCN) by UV light, afforded an excited singlet state species DCN* ($E_{\text{red}}^{\text{S}1} = +2.30$ V vs SCE) able to promote the single electron oxidation of PPh₃ ($E_{1/2} = +0.98$ V vs SCE), affording phosphine radical cation 81. Next, water present in the MeCN reaction solvent, was shown to attack triphenylphosphine radical cation 81 via a two-electron, ionic pathway, affording triphenylphosphoranyl radical 82. Phosphoranyl radical 82 then goes on to form triphenylphosphine oxide via HAT with superoxide, which itself was formed by SET from the reduced state of DCN, thus closing the photocatalytic cycle. Radosevich also observed similar reactivity in a side reaction when investigating racemization of enantioenriched phosphines via a non-photocatalytic SET pathway.²⁸

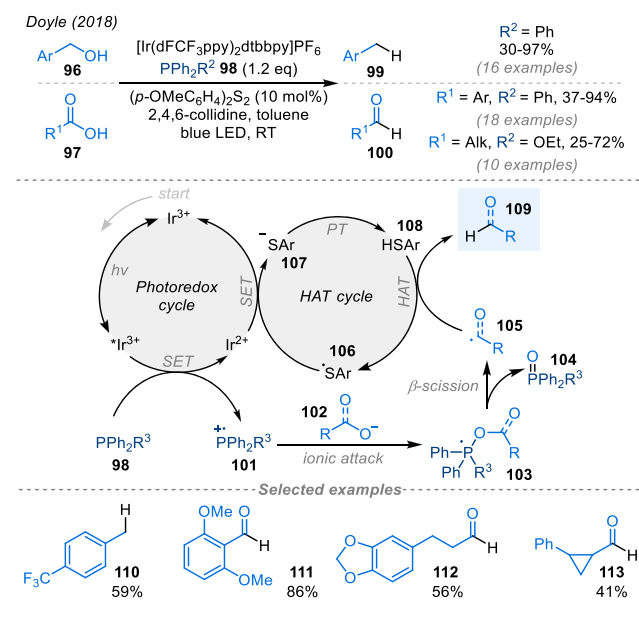
Note that at a very similar time, Yasui and co-workers also observed the formation of triphenylphosphine oxide while investigating the photoreduction of a 10-methylacridinium ion when reacting it with triphenylphosphine, in aqueous MeCN under visible light irradiation (>360 nm), proposing a similar SET mechanism.²⁹ Furthermore, in 2005, Yasui and co-workers conducted synthetic and spectroscopic studies on the photocatalyzed reactions of triarylphosphines with molecular oxygen.³⁰ These reactions also resulted in the formation of the corresponding triarylphosphine oxides, although the group utilized a 9,10-dicyanoanthracene/biphenyl photocatalytic system during these studies.

C–O–*PR₃ Fragmentation. In 2018, Zhu and co-workers reported a direct deoxygenation procedure for the conversion of aryl carboxylic acids 83 into acyl radicals 88 and their subsequent trapping with a series of different alkene radical acceptors 84, to afford a range of aryl ketones 85 (Scheme 12).³¹ The photoexcited iridium catalyst (*Ir³⁺) undergoes

Scheme 12. Aromatic Acyl Radical Alkylation³¹

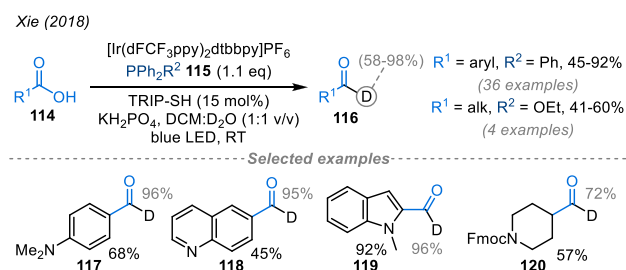
SET oxidation with PPh₃ to form triphenylphosphine radical cation 81. Radical cation 81 can then react ionically with carboxylate anion 86 to generate phosphoranyl radical 87. β-Scission, driven by the thermodynamically favorable formation of triphenylphosphine oxide, generates acyl radical 88, which then selectively attacks alkene 89 to form radical species 90, which can undergo SET with a reductive Ir²⁺ species, thus closing the photocatalytic cycle and affording the corresponding ketone 92. The group demonstrated that a large series of alkene reaction partners worked well in the reaction including vinylpyridines, styrenes, and enone derivatives, in addition to the formation of macrocycles and the late-stage functionalization of bioactive molecules. The group also explored the use of P(*n*Bu)₃ and P(OEt)₃ during the optimization of this reaction; however, both reactions delivered no product. This seminal work provided a new, photocatalytic route for the formation of acyl radicals, a topic that has been reviewed multiple times.³²

Almost concurrently, Doyle and co-workers reported the deoxygenation of benzylic alcohols 96, alongside both, aryl and alkyl carboxylic acids 97 (Scheme 13).³³ Comparable with Zhu's work (cf. Scheme 12), the photoexcited iridium catalyst oxidizes phosphine 98 to afford the phosphine radical cation

Scheme 13. Deoxygenation of Carboxylic Acids/Alcohols³³

101, which then reacts ionically with either an alcohol or carboxylate anion 102 forming phosphoranyl radical 103. However, deviating from Zhu's work, upon β -scission the resultant alkyl or acyl radical 105 undergoes a terminal HAT process with thiol 108 to deliver the corresponding deoxygenated products 109. A final reduction of thiol radical 106 and a proton transfer to thiolate 107 closes both catalytic cycles. Notably, this work extended the scope of the radicals generated from this phosphoranyl radical-mediated process, to include alkyl radicals and aliphatic acyl radicals. The key to unlocking the reactivity of aliphatic carboxylic acids was the use of the phosphinite, Ph_2POEt . It was reported that the use of PPh_3 , which can be employed for the deoxygenation of benzylic alcohols and aromatic carboxylic acids, was ineffective when reacted with aliphatic carboxylic acids. This was accredited to the formation of an electron-rich phosphoranyl radical when reacting PPh_3 with aliphatic carboxylic acids, which was susceptible to single-electron oxidation over the desired fragmentation pathway (cf. Scheme 4). Oxidation of the phosphoranyl radical would afford a phosphonium intermediate capable of rapid acyl transfer. However, when using Ph_2POEt a less electron-rich phosphoranyl radical was afforded and consequently β -scission fragmentation was the predominant reaction pathway observed, delivering the desired aldehyde product.

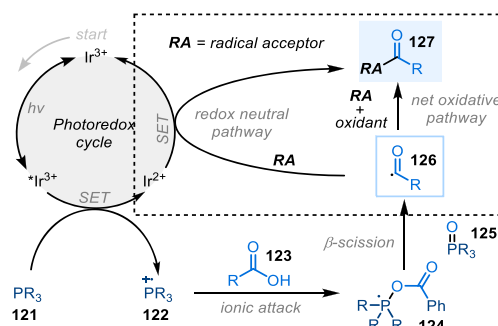
Augmenting the above deoxygenation/HAT process, Xie and co-workers reported a deoxygenation/deuteration protocol³⁴ for carboxylic acids 114, via a process that draws upon Macmillan's³⁵ published radical deuteration and tritiation work (Scheme 14). By performing the deoxygenation/HAT procedure in the presence of a $\text{DCM}:\text{D}_2\text{O}$ solvent system, an exchange process can be established between the proton of a thiol catalyst and the deuterium in D_2O , affording deuterium-labeled thiol, thus serving as the source of deuterium for the acyl radical. The main focus of this study was the deoxygenation/deuteration of aryl carboxylic acids, which were typically afforded in good to excellent yields in most cases tested. In addition, the authors were able to extend the scope of the methodology to include a smaller number of alkyl

Scheme 14. Deoxygenation/Deuteration of Carboxylic Acids/Alcohols³⁴

carboxylic acid starting materials by tuning the phosphine employed in the process.

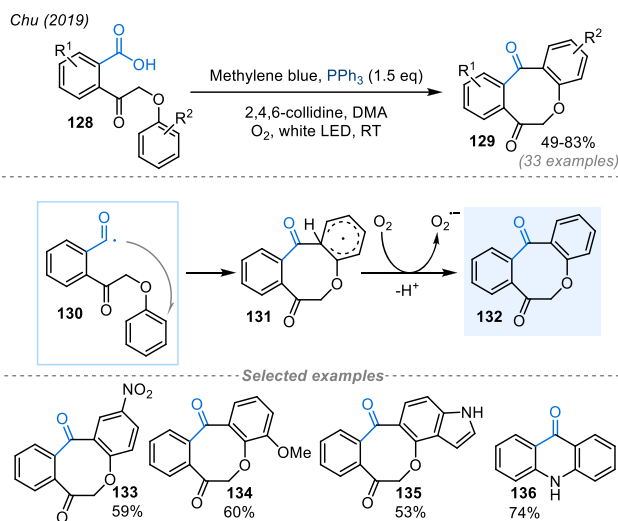
Since these pioneering works (cf. Schemes 12, 13, and 14), there have been a number of expansions to this phosphoranyl radical fragmentation methodology. Most of these studies have focused on the generation of aryl acyl radicals from aromatic carboxylic acids and the subsequent trapping of these acyl radicals with various distinct radical acceptors (represented in generalized form in Scheme 15). Within these studies, the

Scheme 15. General Acyl Radical Functionalization Pathway

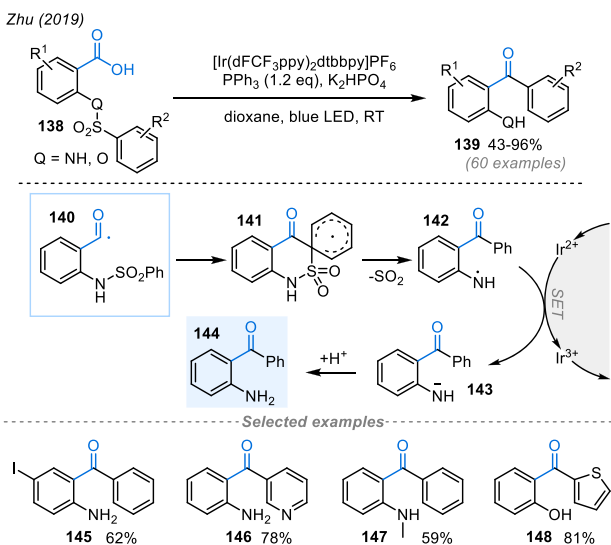


resultant radicals formed from either the inter- or intramolecular addition of acyl radical 126 into a radical acceptor (RA) have been shown to react in one of two ways; either (1) undergo SET reduction from the reduced ground state photocatalyst (for an example see Scheme 12) or (2) undergo oxidation from a stoichiometric oxidant. These studies are presented below (Schemes 16–19); full mechanisms are not presented in these cases, as the initial phosphoranyl radical formation and fragmentation proceeds in broadly the same way, but rather, we have chosen to simply illustrate the outcome of the reactions between the acyl radical and RA, ($126 \rightarrow 127$) as depicted within the dashed box.

In 2019, Chu and co-workers reported the generation of aryl acyl radicals 130 based on a phosphoranyl radical mechanism very similar to that above.³⁶ However, this protocol utilized an organic photocatalyst, methylene blue, as the photoexcited oxidant (Scheme 16). As a result, this protocol is a net oxidative process, using O_2 as the terminal oxidant. Other organic photocatalysts were screened in the reaction but no reactivity was observed. The generated acyl radical 130 underwent intramolecular radical cyclization onto a tethered anisole derivative to afford a range of cyclic products 129. Although the main focus of this procedure was the formation of medicinally relevant benzannulated 8-membered rings,³⁷ other ring sizes (6–7-membered) were synthesized in good to excellent yield.

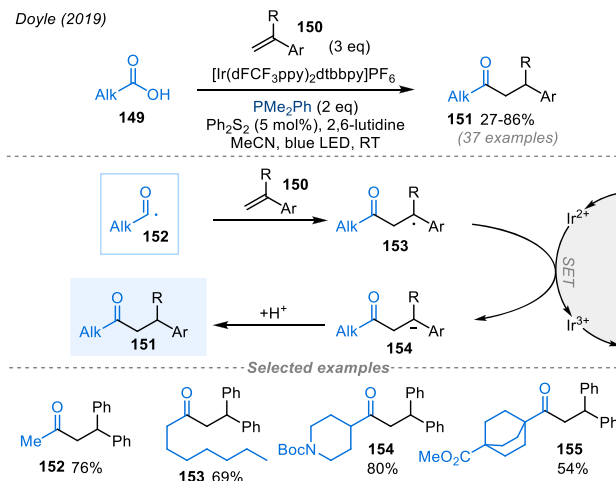
Scheme 16. Intramolecular Acyl Radical Cyclization³⁶

In 2019, Zhu and co-workers reported the generation of aryl acyl radicals **140** (Scheme 17) via the above (cf. Scheme 15)

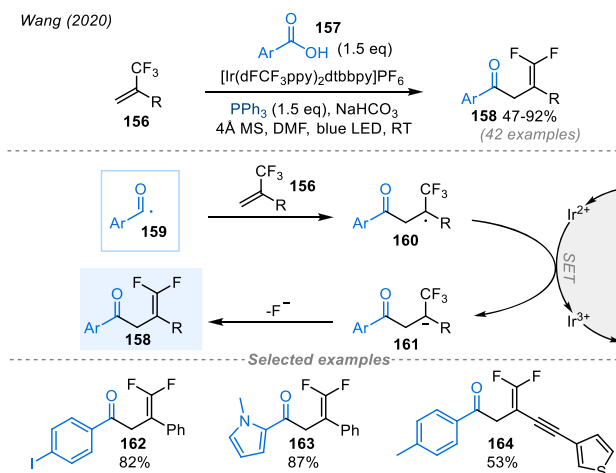
Scheme 17. Intramolecular Acyl Radical Arylation³⁸

phosphoranyl radical method.³⁸ However, in this study, the acyl radical **140** undergoes an intramolecular aryl migration with an appended phenyl sulfonamide, liberating SO₂ gas and affording a range of diaryl ketones **139**.

In 2019, Doyle and co-workers extended the utility of their aliphatic acyl radical-generation methodology (cf. Scheme 13) to include trapping with styrenes as radical acceptors (Scheme 18).³⁹ As before, this process required tuning of the phosphine to enable efficient reactivity with these underexplored aliphatic carboxylic acid starting materials **149**. Upon mechanistic investigation, the use of more electron-rich phosphines (PMe₂Ph and P(*p*-anisole)₃), with lower oxidation potentials were identified as the best reagents to outcompete electron or energy transfer to the alkene radical acceptor **150** from the excited state photocatalyst. PMe₂Ph was identified as the optimal phosphine, ultimately affording an array of aliphatic ketones **151** from aliphatic carboxylic acids **149**.

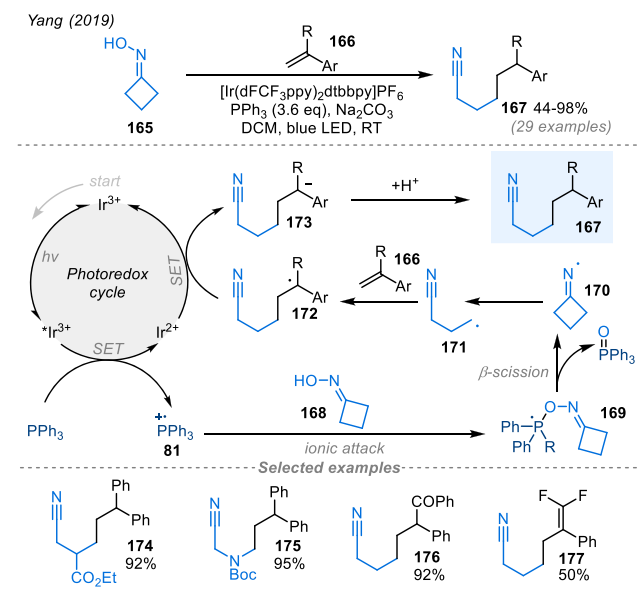
Scheme 18. Aliphatic Aryl Radical Alkylation³⁹

In 2020, Wang and co-workers reported a method whereby they generated aryl acyl radicals **159** by the above (cf. Scheme 15) method and reacted them with α -trifluoromethyl alkenes **156** (Scheme 19).⁴⁰ The subsequent α -trifluoromethyl radical

Scheme 19. Aromatic Acyl Radical Defluorination⁴⁰

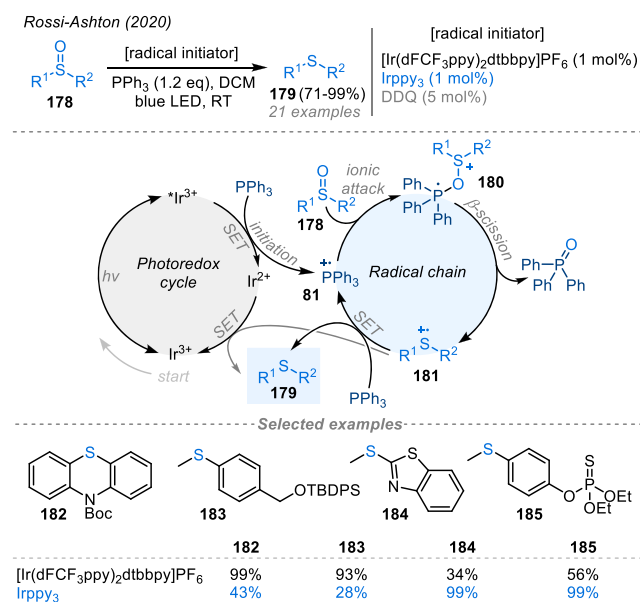
160 undergoes reduction to the anion **161** and then β -fluoride elimination to afford an array of γ,γ -difluoroallylic ketones **158**. The group reported that substrates with strongly electron-withdrawing groups at the *para*-position of the aromatic ring on the carboxylic acid did not afford any product. Equally, a series of aliphatic carboxylic acids were described as unsuccessful substrates.

RN-O-PR₃ Fragmentation. In 2019, Yang and co-workers reported the formation of oxime-containing phosphoranyl radicals **169**, themselves formed from the ionic attack of photocatalytically generated phosphine radical cations **81** by oximes **168** (Scheme 20).⁴¹ Upon β -scission, the phosphoranyl radical **169** would afford triphenylphosphine oxide and iminyl radical **170**. Within this study, cyclobutanone oximes were utilized, and therefore, upon formation of the iminyl radical **170**, a radical transposition occurred through a strain-relieving C-C single bond cleavage to deliver cyanoalkyl radical species **171**. Radical **171** was then trapped with a series of styrenes **166** and α -trifluoromethyl alkenes, affording a range of

Scheme 20. Oxime Deoxygenation/Alkylation⁴¹

elongated cyano **167** and/or gem-difluoroalkene-bearing products. The formation of iminyl radicals from redox active esters has seen great interest in recent years.⁴² This phosphoranyl radical-mediated approach avoids voltage directed derivatizations of oxime starting materials, that are typically required to access these valuable iminyl radicals allowing for a more expedient protocol.

S–O–*PR₃ Fragmentation. More recently, in 2020, Rossi-Ashton and co-workers reported a photocatalytic sulfoxide deoxygenation procedure, proceeding via the formation of phosphoranyl radical **180** (Scheme 21).⁴³ Because of the mild nature of photoredox catalysis, this high-yielding sulfoxide deoxygenation procedure tolerated the reduction of an array of diaryl, dialkyl, and aryl alkyl sulfoxides, including acid-sensitive functionalities that are not compatible with many existing deoxygenation procedures. The authors

Scheme 21. Sulfoxide Deoxygenation⁴³

describe several complementary conditions for this deoxygenation process, each centered around a radical chain mechanism shown in Scheme 21. Upon initiation by a single-electron oxidation, triphenylphosphine radical cation **81** is formed, which undergoes ionic attack from sulfoxide **178**. The resultant phosphoranyl radical **180** undergoes β -scission to expel triphenylphosphine oxide and sulfide radical cation **181**. The sulfide radical cation **181** (e.g., diphenyl sulfide [$E_{1/2} = +1.43$ V vs SCE]) readily undergoes reduction by PPh₃ ($E_{1/2} = +0.98$ V vs SCE), thus propagating the radical chain. When using the highly oxidizing photocatalyst [Ir(dFCF₃ppy)₂dtbbpy]PF₆, typically employed in the above phosphoranyl radical reactions, oxidative initiation occurs from the photoexcited photocatalyst ($E_{1/2}^{\text{red}}[*\text{Ir}^{3+}/\text{Ir}^{2+}] = +0.97$ V vs SCE) and the photocatalytic cycle can be subsequently closed via SET reduction of the sulfide radical cation **181**, affording sulfide **179** and regenerating the ground state photocatalyst (Ir³⁺). Equally, when using substoichiometric (5 mol %) amounts of organic oxidant DDQ, 1-bromo-4-(methylsulfinyl)benzene was deoxygenated in a 96% yield, thus supporting the idea that a phosphine oxidation pathway is active. Interestingly, the deoxygenation process also proceeds in excellent yields when using highly reducing photocatalysts, such as Irppy₃ ($E_{1/2}[\text{Ir}^{2+}/*\text{Ir}^{3+}] = -1.73$ V vs SCE), which do not possess an excited state oxidation potential able to oxidize PPh₃ ($E_{1/2}[*\text{Ir}^{3+}/\text{Ir}^{2+}] = +0.31$ V vs SCE). Furthermore, this photocatalyst was routinely investigated in the optimization of the above phosphoranyl radical reactions with no reactivity reported. In this case, it was proposed that initiation of the deoxygenation process is facilitated by a preceding SET reduction of a sulfoxide-phosphine adduct from the highly reducing excited photocatalyst, thus accessing the oxidized ground state photocatalyst able to initiate the radical chain mechanism via phosphine oxidation.

■ SUMMARY

In summary, photocatalysis, and especially photoredox catalysis, has renewed interest in the generation of radicals via phosphoranyl radical intermediates. The addition of photoredox catalysis to this already established methodology adds considerable advantages, not least enabling the ionic, nucleophilic attack pathway through the ability to maintain a low concentration of oxidizing species during the reaction.

By exploiting the formation of strong P–O/S bonds, as thermodynamic compensation, this method has enabled access to new radical pathways, and hence important new reactivities, that more conventional photoredox catalysis cannot currently access. This is exemplified by the expedient access to acyl or iminyl radicals directly from their corresponding carboxylic acids and oximes, respectively, whereas prefunctionalization strategies are required to access the analogous radical species when using nonphosphoranyl radical-mediated photoredox catalysis. Furthermore, the mild conditions achievable using this phosphoranyl radical/photoredox combination has enabled greater substrate tolerance relative to corresponding nonradical pathways, exemplified by the mild deoxygenation of sulfoxides containing acid-labile groups.

However, despite the intriguing possibilities of this radical generation method, a significant portion of the recent literature has focused on exploring the scope of aromatic acyl radicals, which are formed from the corresponding carboxylic acids via phosphoranyl radical intermediates. Perhaps of greater interest is the range of radicals that could be generated using this

phosphoranyl radical method, beyond aromatic acyl radicals. Indeed, the potential of this approach has already been partly demonstrated by innovative studies focusing on more diverse radicals including, benzylic radicals, aliphatic acyl radicals, as well as iminyl and sulfide radicals.

This said, there is still much room for the development of this methodology; given the long history of traditional radical chemistry, especially considering the extensive mechanistic work, conducted by Bentrude and others in the late 20th century, there are certainly many more deoxygenation and desulfurization pathways that can be conceived and should be readily accessible. Additionally, current methods result in significant waste, primarily the stoichiometric formation of phosphorus oxide species; the development of photocatalytic processes which are catalytic in the phosphorus species would no doubt extend their application in organic synthesis. Such an advance would undoubtedly be a major challenge to achieve, although recent breakthroughs in the use of catalytic amounts of phosphorus in the Mitsunobu reaction provide encouragement that this challenge is not insurmountable.⁴⁴ Accordingly, development of these processes will no doubt be facilitated by a better understanding of the formation and reactivity of phosphoranyl radical intermediates.

It is evident that PPh₃, the most commonly employed phosphorus species in this methodology, is not optimal for all processes (cf. Doyle's works, Schemes 13 and 18), a fact that is particularly pronounced when forming aliphatic acyl radicals from carboxylic acids. Additionally, the photocatalyst employed can have considerable impact on the functional group compatibility of the reaction (cf. Rossi-Ashton's work, Scheme 21). Accordingly, when designing a new phosphoranyl radical-mediated reaction, three important mechanistic elements should be considered to best enable both the formation (Scheme 3) and reactivity (Scheme 4) of the phosphoranyl radical intermediate to occur in a selective manner:

- (1) *Phosphine derivative*: By tuning the structure of the phosphine derivative, one can promote the selective oxidation and thus avoid competing photocatalyst redox activity with other starting materials. Additionally, tuning can be used to avoid unwanted reactivity pathways of the phosphoranyl radical, thus enabling the selection of a single phosphoranyl radical reactivity pathway (e.g., β -scission). Note that these features may work in opposing fashions, and therefore, correct balancing may be required; for example, lowering the oxidation potential of the phosphine derivative (to promote selective formation of the phosphoranyl radical)³⁹ may result in the subsequent phosphoranyl radical being too electron-rich and consequently promote undesired oxidation reactivity pathways over fragmentation.³³
- (2) *Photocatalyst*: With judicious choice of the photocatalyst, much like the point above, one can more precisely marry the redox window of the photocatalyst to the phosphine derivative, while also considering other functionality present within the reaction.⁴³
- (3) *Radical chain mechanism*: With better recognition of the importance of radical chain processes, of the type that are evident in several of the reactions reported in this Perspective, one can more accurately optimize the overall phosphoranyl radical-mediated transformation. The importance of radical chain processes is sometimes

overlooked,⁴⁵ especially in the field of photoredox catalysis, where closed cycle mechanisms, that rely on the photocatalyst to mediate reactivity throughout, are commonly proposed instead. Thus, taking effort to properly ascertain the dominant mechanism in processes such as these is critical in facilitating continued progress and understanding in this field.

Phosphoranyl radical intermediates have already shown themselves to be extremely valuable reactive intermediates in synthetic chemistry. By continuing to combine our extensive knowledge of radical chemistry from the past, with an advanced understanding of the generation and reactivity of phosphoranyl radical intermediates, alongside adding in the constantly evolving advances in photoredox catalysis, this photocatalytic phosphoranyl radical methodology will continue to open up new innovative radical reactivity and display its great utility.

AUTHOR INFORMATION

Corresponding Author

James A. Rossi-Ashton – Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.; orcid.org/0000-0002-0989-2506; Email: james.rossiashton@york.ac.uk

Authors

Aimee K. Clarke – Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

William P. Unsworth – Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.; orcid.org/0000-0002-9169-5156

Richard J. K. Taylor – Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acscatal.0c01923>

Notes

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